Unusual intraoral cancer with unexpected outcome in a patient with xeroderma pigmentosum: An alert for antineoplastic treatment

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Xeroderma pigmentosum (XP) is a rare autosomal disorder characterized by extreme sensitivity to ultraviolet radiation. DNA repair mechanisms are impaired, and minimal sun exposure can lead to the development of cutaneous neoplasms in very young patients. Intraoral carcinomas are uncommon and, when present, are located mainly at the tongue tip. We report an unprecedented case of squamous cell carcinoma (SCC) in the floor of mouth of a 23-year-old woman with XP. The patient was referred to the oncologist, and 2 months after surgical resection, she underwent a single session of chemotherapy plus radiotherapy. However, she died 73 hours after undergoing her first chemotherapy session. Considering the unexpected outcome of this case, we also investigated possible exacerbated adverse effects of antineoplastic treatments (especially cisplatin-based chemotherapy) in patients with XP and reviewed the main characteristics of the disease, especially cases with oral manifestations reported in the literature. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:e1–e11)

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder, in which DNA damages are difficult to repair, and the disorder is mainly caused by the ultraviolet (UV) radiation.[1] In the very first decades of life, patients develop numerous malignant skin neoplasms.[1,2] The skin on both the head and the neck is generally affected, and patients have a higher risk of developing lower lip and tongue tip cancer (areas most exposed to UV radiation). Moreover, these patients have a 10 to 20 times higher risk of developing inner neoplasms that do not have a UV etiology, suggesting that the repair of the oxidative damage to the endogenous DNA could also be deregulated.[3]

The disease has a severe course, and about two-thirds of patients are unaware of their own condition and/or do not apply preventive measures.[3] Early diagnosis is very important to prevent malignant complications, which are the main causes of death. In addition, the literature speculates on possible exacerbation of adverse effects when certain antineoplastic drugs, such as cisplatin, are used in these patients.[4] Considering that intraoral lesions are uncommon, the aim of this report is to describe a case of squamous cell carcinoma (SCC) on the floor of the mouth of a 23-year-old woman with XP, whose response to treatment progressed in a severe and unexpected way. In addition, the oral manifestations of XP reported in the literature, as well as the influence of antineoplastic treatment on the clinical course of the disease, are analyzed.

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CASE REPORT

A 23-year-old woman with a previous diagnosis of XP was referred to the UEM Dental School with a complaint of "macula and sore in the mouth", of 8 months' of evolution. She had a family history of consanguineous marriage of parents and a brother with XP, who underwent lower lip resection. Both the patient and her brother had been diagnosed with XP in their childhood. She denied neurologic disturbances and prior surgical procedures. Weak photophobia and numerous hyperpigmented ephelides throughout the body were observed, as well as a melanocytic nevus in the region of the right eyebrow (Figure 1). No lymphadenopathy was observed.

Intraoral examination revealed a painless endophytic ulcer on the floor of the mouth, with a hardened base and yellowish-white borders, measuring approximately 2 cm (Figure 2A). In addition, a 4-cm verrucous white plaque was present at the tip and borders of the tongue, with diffuse limits and focal area of erythema and ulceration (Figure 2B).

On the basis of the clinical findings, presumptive diagnoses of SCC in the floor of the mouth and leukoplakia or erythroleukoplakia in the tongue were hypothesized. Incisional biopsy of the lesion followed by histopathologic examination showed neoplastic parakeratinized squamous epithelium, with extensive connective tissue infiltration. The muscular plane was also involved. Numerous dyskeratotic foci indicating loss of stratification were seen, and in neoplastic nests, malignant epithelial cells exhibited pleomorphism, hyperchromatism, and atypical mitoses (Figure 3), confirming the diagnosis of SCC. In the tongue lesion, a hyperorthokeratinized stratified squamous epithelium with associated hypergranulosis was present. In the lower layers, pleomorphism, hyperchromatism, and areas of

Fig. 1. Extraoral examination. Multiple hyperpigmented ephelides throughout the body.

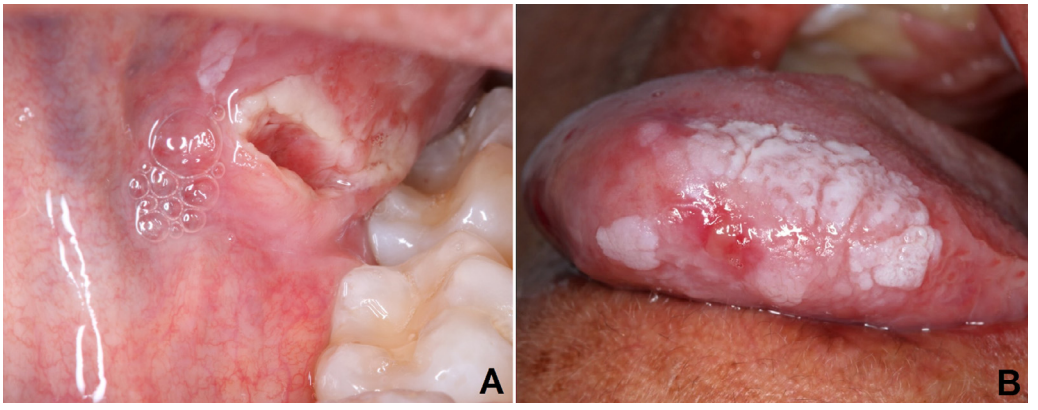

Fig. 2. Intraoral examination. **A**, Endophytic ulcer on the floor of the mouth, with hardened base and yellowish-white border. **B**, Verrucous white plaque at the tip and borders of the tongue, with diffuse limits and a focal area of erythema and ulceration.

inverted polarization were present (Figure 4). Thus, a diagnosis of hyperkeratosis with discrete atypia, compatible with the clinical diagnosis of leukoplakia, was established.

The patient was referred to an oncologist, who performed excision of the malignant lesion, 3 months after the diagnosis. Resection of the cervical ganglia was also done. After 2 months, at 10 a.m. on a Friday, the

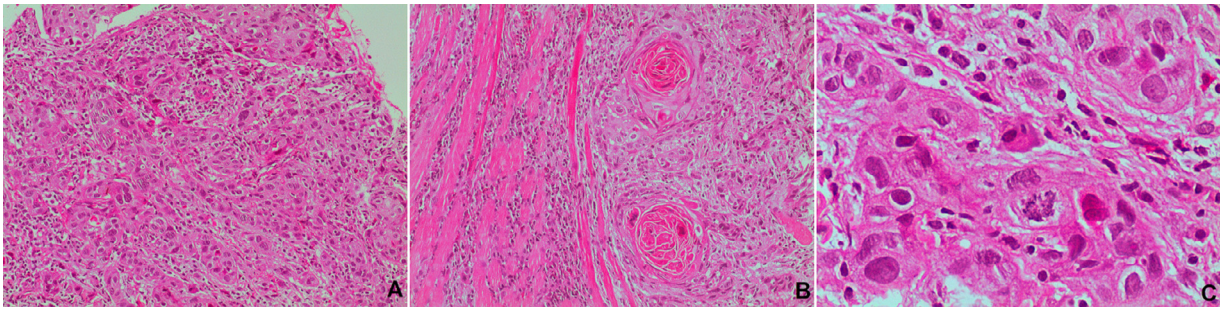

Fig. 3. Photomicrographs of the lesion on the floor of the mouth. **A**, Neoplastic parakeratinized squamous epithelium advancing and blending into the underlying connective tissue (hematoxylin and eosin [H&E]; original magnification × 10). **B**, Dyskeratotic foci and muscular infiltration (H&E; original magnification × 10). **C**, Neoplastic nests of malignant epithelial cells exhibiting pleomorphism, hyperchromatism and atypical mitoses (H&E; original magnification × 40).

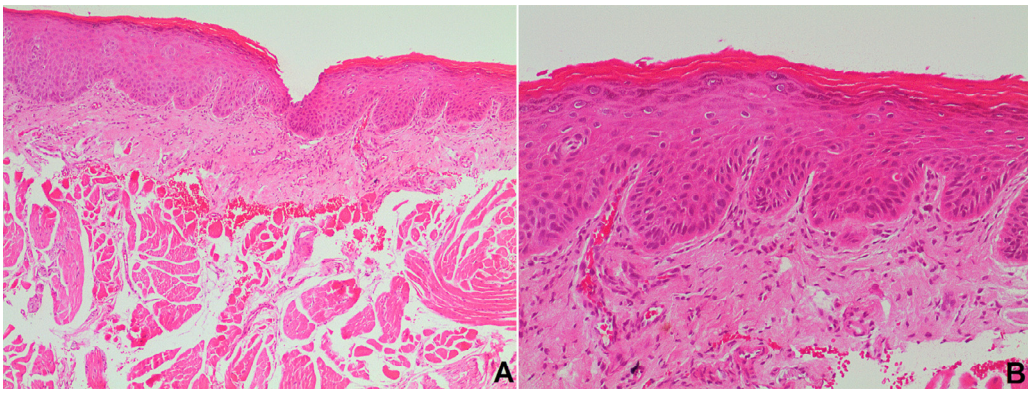

Fig. 4. Photomicrographs of the lesion on the tongue. A, Hyperorthokeratinized stratified squamous epithelium with associated hypergranulosis, with maintenance of stratification and absence of submucosal invasion (hematoxylin and eosin [H&E]; original magnification × 4). B, The lower layers showing pleomorphism, hyperchromatism, and inverted polarization in some points (H&E; original magnification × 10).

patient underwent a 180 cGy radiotherapy session (planned: 50.4 Gy (28 × 180 cGy) + 200 cGy dose boost (planned: 20 Gy [10 × 200 cGy]). At 1:30 p.m., she underwent the first chemotherapy session with 50 mL of cisplatin 50 mg. Soon after the therapy session, the patient went home. The next day, at 1 p.m., diarrhea, nausea, and vomiting started, but the patient did not seek medical help. On Sunday, her condition got worse and she was taken to the hospital emergency department.

The patient was admitted to the intensive care unit at 6:50 a.m. Monday with impaired renal function and with high levels of urea and creatinine. The patient was conscious and responsive, but tachycardic and dyspneic, and she received oxygen supplementation via catheter. With reduced vesicular murmurs, no adventitious noises, preserved peripheral perfusion, and poor diuresis via a Foley catheter, the patient progressed to significant metabolic acidosis and acute renal and respiratory failure. She was intubated around 11:40 a.m. on Monday. A central venous catheter was used for vasoactive drug administration, and hemodialysis was started. The patient's condition deteriorated, with 2 cardiorespiratory arrests in the morning, which were reversed; and motor and respiratory physiotherapies were provided subsequently. In the afternoon, the patient's condition worsened again with cardiorespiratory arrest. Attempts at cardiopulmonary resuscitation were unsuccessful, and the patient died at 2:30 p.m.

Comparative analysis of published cases of oral lesions in patients with XP

A review of the English-language literature, from 1983 to 2019, revealed 156 documented cases of oral manifestations in patients with XP. The search was conducted in the PubMed database, using the terms "xeroderma pigmentosum" AND "oral cancer" OR "oral lesion". A complementary search in Google Scholar and a manual one in the references lists of the selected papers and yielded 22 additional manuscripts. Only case reports and case series that included oral manifestations were used in this comparative analysis. Sixty-six papers met the inclusion criteria, totaling 232 lesions, in 166 patients. The data of these cases, as well as that of the new one presented here, are summarized in Appendix I.

DISCUSSION

When patients with XP are exposed to UV radiation, their cells mutate at a high rate, and repair of mutated DNA also becomes difficult. As a result of this extreme sensitivity to UV radiation, patients suffer severe burns, even with minimal exposure. In early childhood, patients exhibit hyperpigmented macules on the skin.[1,2] Some UV-induced eye changes, such as photophobia, severe corneal inflammation, eyelid skin atrophy, tearing, keratitis, and opacity, may also appear prematurely. Subsequently, cornea and eyelid tumors may occur.[5,6] Neurologic alterations are found in approximately 25% of the cases.[1,2,6,7] Acquired microcephaly, progressive intellectual dysfunction, sensorineural hearing loss caused by high frequencies, spasticity, ataxia, and/or convulsions have been reported.[8,9] XP usually manifests in the first 2 years of life and has no gender predilection.[10] Our patient reported that both she and her brother were diagnosed in the first decade of life. Both had the characteristic sign of the disease (thus the name xeroderma pigmentosum, which literally means pigmented and dry skin) and photophobia. No ocular or neurologic involvement was reported.

Over time, patients with XP have a significantly increased risk for various malignancies, such as SCC, basal cell carcinoma and melanoma, in addition to

other nonneoplastic abnormalities.[10,11] The clinical presentation may vary, as well as the prognosis, depending on the type of mutation and the amount of sun exposure.[8,12-15] Intraoral lesions are unusual. Our search resulted in the identification of 166 patients (age 10 months to 82 years). We found 115 cases of SCC: tongue (52), lip (41), gingiva (3), buccal mucosa (1), maxilla (1), palate (1), location not reported (16), and our case, the first described in the floor of the mouth. There were also 8 cases of basal cell carcinoma of the lip; 3 of intraoral melanoma (2 in the lip and 1 in the tongue); 2 cases of angiosarcoma (1 in the tongue tip and 1 in the parotid gland); 2 malignant schwannoma of the trigeminal nerve; 1 fibrosarcoma in the border of the tongue; 1 trichilemmal carcinoma in the upper lip; and others (100) (see Appendix I). As can be seen, there is an increased risk of growth of epithelial tumors in these individuals,[11] although nonepithelial neoplasms have also been reported. Some studies[11] that used cell cultures have shown that skin fibroblasts are more sensitive to UV radiation and to some chemical carcinogens in patients with XP.

The present case illustrates, for the first time, invasive SCC in the floor of the mouth. Our search resulted in other 6 SCCs in areas not exposed to UV, such as the gingiva (3), buccal mucosa (1), maxilla (1), and palate (1). Mutations in the p53 gene,[16] as well as failures in immune surveillance,[17,18] may explain the occurrence of malignancies in these areas. Studies have shown decreased interferon -γ production and natural killer cell activation, as well as reduced numbers of circulating T cells in patients with XP.[17-19] Furthermore, the CD3+/CD4+ ratio in circulating lymphocytes is typically reduced in these patients.[17,18]

It is also important to consider that patients with XP have mutations in 1 of 7 genes (XP-A through XP-G)[20] and that XP completion group C (XP-C) is one of the most common forms.[21] XPC is an important protein in the altered DNA repair process, mainly because it helps in the recognition of damage.[22] Failures in XP-C are associated with various cancers.[23,24] In patients with XP, for example, it may be defective, making it difficult to correct the damage, thus inducing cancer, even in areas not exposed to UV radiation.[25] Therefore, the XP-C protein protects the cell from malignant transformation. If defective, it cannot play this protective role.

Generally, in individuals without XP, oral cancer develops after the fifth decade of life, especially in alcoholics and smokers, and the border of the tongue is the most affected area. In patients with XP, cancer develops more prematurely, as in the present case, in which the patient was only 23 years old. The association with UV radiation is obvious, justifying the high frequency of lesions in the lower lip and the tongue tip,[3,6,26-28] as demonstrated in this review. However, because of the difficulty in repairing mutated DNA, many years of cumulative UV exposure is not necessary for the development of cancer in these individuals.

There is no cure for XP, but early diagnosis and immediate implementation of UV protection help extend the individual's life.[3,7] Gene therapy is still in an experimental stage, but genetic counseling is recommended.[10] Malignant lesions can be treated with surgery or cytotoxic drugs.[10] Radiotherapy has been considered an alternative when surgery is potentially mutilating[29]; however, caution should be exercised with regard to its use because cellular radiosensitivity in these patients seems to be atypical.[30]

The fact that our patient died 3 days after a single session of chemotherapy plus radiotherapy led us to investigate possible causes of death. Cisplatin—a chemotherapeutic agent widely used in antineoplastic treatments—has cytotoxic effects, acting through the formation of intracellular adducts of DNA that block its replication and induce apoptosis.[4,31] Normal cells are usually protected by DNA repair mechanisms, so this effect is mainly verified in malignant cells; however, the normal cells of patients with XP are not able to do the same. Therefore, some authors[4,32] have suggested that treatment with cisplatin may cause severe adverse effects on the normal cells of patients with XP and should be avoided.

In fact, cisplatin is an antineoplastic agent that acts primarily on malignant cells, damaging their DNA and inducing apoptotic death.[31] The XP-C protein seems to be unable to repair the damage caused by cisplatin in malignant cells because of the magnitude of the damage. However, XP-C can protect normal cells from concomitant apoptotic death by repairing the damage caused by chemotherapy. Thus, XP-C would act to improve chemotherapy selectivity, preventing the loss of normal cells. However, in patients with XP, who are potential carriers of defective XP-C,[20] this mechanism of reversal of damage caused by chemotherapy in normal cells is compromised, and thus, normal cells may also undergo apoptosis. Depending on the degree of disability of XP-C[20] and the resulting number of lost cells, cisplatin can cause death, especially as a result of renal failure because the urinary tract is the main route of drug elimination.[33] Thus, XP-C would represent an important biomarker, not only for cancer prevention and diagnosis but also to guide treatment.

Sumiyoshi et al.[4] reported 2 cases of XP with lung and esophageal cancers, where patients experienced serious adverse events, including multiple organ failure, after cisplatin-based chemotherapy. Both patients presented 1 week after chemotherapy with rapid ototoxicity and very acute kidney injury, which demanded hemodialysis. The authors speculated whether the other chemotherapeutic agents (vinorelbine and 5-

fluorouracil) could have induced these events. However, ototoxicity is characteristic of platinum-containing agents, such as cisplatin.[34] Moreover, acute kidney injury is a dose-limiting toxicity of cisplatin and needs a large amount of fluid replacement for prevention. It is rarely observed in treatments with other drugs, such as 5-fluorouracil and vinorelbine.[4] The cytotoxic mechanisms of these drugs are not directly associated with DNA repair systems, suggesting that the severe adverse events in patients with XP probably result from cisplatin use.[4] These data were reinforced when we observed that our patient's condition deteriorated very similarly after being treated with cisplatin alone.

These reports, although scarce, are timely and reinforce the importance of careful planning of the antineoplastic approach and the need for a guideline regarding the use of DNA-damaging agents in patients with XP. We emphasize that the choice of treatment should be made by a multidisciplinary team. The present case, together with the 2 previous reports, is not enough to affirm that cisplatin is contraindicated in patients with XP. In addition, we could not determine whether the associated radiotherapy session could have contributed to the outcome of our case, mainly because our patient underwent only 1 radiotherapy session. There is no strong scientific evidence in the literature that radiotherapy may interfere with the prognosis of patients with XP, although some authors have stated that the cellular radiosensitivity of these patients seems to be atypical.[30] We did not find other possible factors that explained the prognosis of these cases. From our point of view, all these data are still speculative, but they represent an alert. Practitioners should be aware that cisplatin may potentially induce serious adverse effects in patients with XP.

CONCLUSIONS

The pathogenesis of oral malignant neoplasms in patients with XP is still uncertain, especially when lesions develop in areas not exposed to UV radiation. In these situations, immunologic surveillance may be compromised. The disease is a severe one, and inappropriate management may worsen the prognosis. Cisplatin chemotherapy has been identified as a potentiator of adverse effects, such as acute renal toxicity. It is of primary importance for dental surgeons, dermatologists, ophthalmologists, neurologists, geneticists, and oncologists to be knowledgeable about the features of XP to help prevent injuries caused by UV exposure and to perform early diagnosis and careful planning of antineoplastic treatments in patients with cancer. A multidisciplinary approach is extremely important and increases survival rates.

PRESENTATION

This case was presented at the 45th Brazilian Congress of Oral Stomatology and Pathology in Maceió-AL, Brazil.

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APPENDIX I. PREVIOUSLY REPORTED CASES OF ORAL LESIONS IN PATIENTS WITH XP

Authors (year)	*Number of cases*	*Age (years)*	*Sex*	*Location*	*Diagnosis*	*Treatment*	*Outcome*
Yagi et al., 1983[35]	1	14	N.I.	Tongue tip	SCC	N.I.	N.I.
Kawano et al., 1983[36]	1	9	N.I.	Lower lip	SCC	Excision	Good
Hiraga et al., 1983[37]	1	60	N.I.	Lower lip	SCC	Radiotherapy and bleomycin	Good
Yamaguchi et al., 1984[38]	1	29	N.I.	Lower lip	SCC	Bleomycin	Good
Kenyon et al., 1985[39]	1	46	F	Upper lip	SCC	Excision and radiotherapy	Bad
Wade and Plotinick, 1985[40]	2	10/12	F/M	Tongue tip Lip	SCC (2 tongue) SCC (2 lip)	Excision and hemiglossectomy	Bad
Roytta and Anttinen, 1986[41]	1	32	F	Lower lip	SCC	N.I.	Death
Osguthorpe and Lang, 1987[42]	1	28	N.I.	Upper Lip	SCC	Cisplatin, etoposide, cyclophosphamide	Death
Ohara et al., 1987[43]	1	52	N.I.	Lower lip	SCC	Excision	Good
Ashall et al., 1987[44]	1	9	M	Lip	BCC	Excision	8-month follow-up
Kraemer et al., 1987[6]	32	N.I.	N.I.	Tongue tip (13); gingiva (2); palate (1); N.I. (16)	SCC (32)	N.I.	N.I.
Karja et al., 1988[45]	1	7	F	Tongue	SCC	Excision	Good
Aledo et al., 1989[46]	3	N.I.	N.I.	Lip	SCC (2) BCC (1)	N.I.	N.I.
Keukens et al., 1989[47]	1	9	M	Tongue	SCC	Etretinate, indomethacin and prednisolone	Death
Ikeshima et al., 1990[48]	1	24	N.I.	Maxilla	SCC	Bleomycin, excision, radiotherapy and picibanil	Death
Robbins et al., 1991[49]	1	15	M	Lip	Angular cheilitis	N.I.	N.I.
Patton and Valdez, 1991[50]	1	44	F	Lip	SCC	Excision	Good
Nakamura et al., 1991[51]	1	43	M	Trigeminal nerve	Malignant Schwannoma	Resection	N.I.
Khatri et al., 1992/ 1999[52,53]	38	±8	N.I.	Lip (33) Tongue (20) Buccal mucosa (17)	Lips (28 cheilitis, 2 cutaneous horn, 1 BCC, 2 SCC); tongue (13 erosion, 5 papilloma, 2 hemangiomas, 1 precancerous growth, 1 SCC); buccal mucosa (12 erosion, 4 gingivostomatitis, 1 papilloma)	N.I.	N.I.
Agrawal et al., 1992[54]	2	12/10	M/F	Tongue	SCC (2)	Excision	Good
Salob et al., 1992[55]	1	9	F	Lip and tongue	Hyperpigmentation	Fluorouracil, oral etretinate	Good
Berth-Jones et al., 1993[56]	1	66	M	Lower lip	SCC	N.I.	Good
Yamashiro et al., 1994[57]	1	46	M	Trigeminal nerve	Malignant Schwannoma	Resection	Good
Rosin et al., 1994[58]	2	23/22	M	Tongue	SCC (2)	Excision	N.I.
Goyal et al., 1994[59]	2	5/7	F/M	Tongue tip	SCC (2)	N.I.	N.I.
Chi et al., 1994[60]	1	61	F	Lower lip	SCC	Excision	5-month follow- up
Itoh et al., 1995[61]	1	18	F	Upper lip	BCC	Excision	N.I.

(*continued*)

APPENDIX I. *(Continued)*

Authors (year)	*Number of cases*	*Age (years)*	*Sex*	*Location*	*Diagnosis*	*Treatment*	*Outcome*
Masinjila and Arnbjornsson, 1998[62]	2	1/5	M/F	Tongue Lip and tongue	N.I. (tongue) Malignant melanoma (1 lip; 1 tongue)	N.I. (tongue) Excision (lip and tongue)	N.I.
Jacky, 1999[63]	5	±7	N.I.	Tongue tip	SCC (5)	N.I.	N.I.
Youssef et al., 1999[64]	1	6	F	Lip	SCC	Excision	N.I.
Saade et al., 1999[65]	1	5	M	Upper lip	SCC	Isotretinoin and chemotherapy	Lost follow-up
Dilek et al., 2000[66]	1	5	M	Lower lip	Atypical fibroxanthoma	Topically fluorouracil and tretinoin cream	20-month follow-up
Kawauchi et al., 2000[67]	1	49	N.I.	Lower lip	SCC	Excision and peplomycin	Good
D'Errico et al., 2000[68]	1	12	M	Lip	BCC	N.I.	N.I.
Akan et al., 2001[69]	1	17	N.I.	Upper lip	SCC	Excision	Good
Roseeuw, 2003[70]	1	15	F	Upper lip	BCC	Imiquimod 5% cream	18-month follow-up
Bhutto et al., 2005[71]	2	14/10	M	Lower lip Lip	SCC (lower lip) Ulcer (lip)	N.I.	N.I.
Chidzonga, 2005[72]	2	3/5	F/M	Lower lip	SCC (2)	Excision and radiotherapy	Death within 10 months
Hiramoto et al., 2007[73]	1	82	M	Lower lip	SCC	Peplomycin	Good
Patil et al., 2007[74]	1	13	M	Upper lip	SCC	Excision	Death within 2 years
Saraiya et al., 2007[75]	2	8/9	M	Lower lip	SCC (2)	Excision	N.I.
Mahindra et al., 2008[28]	1	23	M	Tongue tip	SCC	Excision	Good
Chidzonga et al., 2009[26]	9	±6	F (7) M (2)	Tongue tip (6); upper lip (2); lower lip (1); tongue dorsum (5); border of tongue (2)	SCC (13 tongue; 3 lip) Fibrosarcoma (1 border of tongue)	N.I.	Good (1); death within 15 years after diagnosis (1); lost follow-up (5); N.I. (2)
Feller et al., 2010[3]	1	19	F	Lip Tongue	Severe actinic cheilitis (lip) Erosion (tongue)	Palliative treatment	3-month follow-up
Butt et al., 2010[27]	4	±14	M	Lip (3); tongue (4)	SCC (2 tongue; 2 lip) Pyogenic granuloma (2 tongue; 1 lip)	Excision (2) Vermilionectomy (1) N.I. (2)	Good (1) Follow-up (2) N.I. (1)
Mane et al., 2010[76]	1	25	M	Upper lip	Trichilemmal carcinoma	None	Lost follow-up
Alfawaz and Al-Hussain, 2011[77]	1	N.I.	N.I.	Tongue	SCC	N.I.	N.I.
Grampurohit et al., 2011[78]	1	18	M	Lip	Malignant melanoma (upper lip) SCC (lower lip) BCC (upper lip)	Excision	Bad
Hasan and Khan, 2011[79]	1	18	M	Gingiva Tongue	Gingival desquamation Fissuring and geographic tongue	Oral hygiene instruction and use of topical triamcinolone acetonide	3-month follow-up
Beogo et al., 2012[80]	1	7	M	Lower lip	SCC	N.I.	Lost follow-up
Anand et al., 2012[81]	1	40	F	Lip	SCC and depigmentation	N.I.	N.I.
Karkouche et al., 2013[82]	1	27	F	Parotid gland	Angiosarcoma	Resection	Good
Olson et al., 2012[83]	1	11	F	Tongue tip	Angiosarcoma	Excision and Radiotherapy	Bad
Shams et al., 2014[84]	1	25	M	Lip	BCC (lower lip) Cavernous hemangioma (upper lip)	Excision	Bad

(continued)

APPENDIX I. *(Continued)*

Authors (year)	*Number of cases*	*Age (years)*	*Sex*	*Location*	*Diagnosis*	*Treatment*	*Outcome*
Karass et al., 2014[18]	2	8/8	F	Lip (2) Tongue (1)	SCC (2 lip) Actinic keratosis (1 lip) Pyogenic granuloma (1 tongue)	N.I.	Death within 16 years after diagnosis(1); N.I. (1)
Machado et al., 2014[85]	1	11	M	Tongue tip	SCC	Excision	N.I.
Halkud et al., 2014[86]	4	±3	F (3) M (1)	Lip	Fissuring (2) Hyperpigmentation (2) Whitening (2)	N.I.	N.I.
Bologna et al., 2014[87]	4	±15	F (3) M (1)	Tongue tip	SCC (1) Pyogenic granuloma (3) Atrophic lesion (4)	Excision	Good
Wayli, 2015[10]	1	29	F	Tongue dorsum	Pyogenic granuloma	Excision	N.I.
Coulombe et al., 2015[88]	1	8	F	Tongue tip Gingiva	SCC (1 tongue; 1 gingiva)	Radiotherapy and chemotherapy	Death within 15 months
Kraemer et al., 2015[89]	1	2	F	Upper lip	SCC	N.I.	N.I.
Abdullahi et al., 2015[90]	1	7	M	Antero-lateral part of the tongue	SCC	Radiotherapy	Lost follow-up
Dawe and McGuire, 2017[91]	1	62	F	Lip	SCC	N.I.	N.I.
Fife et al., 2017[29]	1	8	M	Lower lip	Atypical melanocytic hyperplasia	Hedgehog inhibitor vismodegib	21-month follow-up
Tadke et al., 2017[92]	1	17	F	Lower lip	SCC	Excision	6-month follow-up
Kajal and Agrawal, 2019[93]	1	12	M	Lip Tongue Buccal mucosa	SCC (1 lip; 1 tongue; 1 buccal mucosa)	N.I.	N.I.
Present case	1	23	F	Mouth floor Tongue tip	SCC (mouth floor) Leukoplakia (tongue tip)	Excision, radiotherapy and chemotherapy	Death within 6 months
Total	167						

M: male; F: female; SCC: Squamous cell carcinoma; BCC: Basocellular carcinoma; N.I.: Not informed; Bad outcome: When there is recurrence of lesion or treatment was not effective; Good outcome: Good prognosis, just follow-up.